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10/713,808	11/14/2003	Dave S.B. Hoon	89212.0014	4483

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EXAMINER

AEDER, SEAN E

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/713,808	HOON ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 3 and 14-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2 and 4-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

The Election filed 1/20/06 in response to the Office Action of 10/20/05 is acknowledged and has been entered. Applicant elected group I and the marker gene MART-1 with traverse.

The traversal is on the ground(s) that limiting claim 2 to a single gene would exclude methods of detecting various combinations of genes. Applicants argue that the genes listed in claim 2 are closely related as melanoma-associated genes. Thus, Applicants assert that the status in the art and the field of search for each of the genes largely overlaps and searching all the genes of claim 2 would not cause a serious burden on the Examiner. Applicants further argue that since claim 3 only recites specific embodiments of claim 2, it would place no additional burden on Examiner to include claim 3 in group I. Applicants further assert that the marker genes recited in claim 3 are closely related as being melanoma-associated genes and that the status in the art and the field of the search for each of the genes largely overlaps. Therefore, because limiting claim 2 to one gene would exclude methods of detecting various combinations of genes in group I and because an asserted relationship between the genes within claims 2 and 3 would result in an overlapping search of all genes, Applicants argue that searching groups I-V together and groups VI-IX together would allow inclusion of all possible combinations of genes recited in the claims and would not result in a serious search burden for the Examiner. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are

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independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in the Office Action. *Methods comprising detecting different combinations of genes are distinct inventions* with different method steps and reagents used. Thus, limiting the invention of group I to a single gene from claim 2 allows the Applicant to identify a distinct invention. It is noted that each of the possible combinations can be found in the various groups. Further, a search of one gene of claim 2 would not result in a sufficient search for every other gene of claim 2. Thus, performing a complete search for all the genes of claim 2 together would result in a serious burden for the examiner. Further, searching all the combinations of the genes of claim 2 (claim 3) in group I would result in a serious search burden. Combining groups I-V and VI-X and searching and examining distinct methods together would result in a serious burden on the examiner. Furthermore, it is noted that the literature search, particularly relevant in this art, is not coextensive and is very important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

The requirement to select a species has been withdrawn by Examiner.

Due to an overlap in the search with the elected invention of MART-1, groups II and V have been rejoined with elected group I. This broadens the elected invention to include the genes tyrosinase and MAGE-A3.

Claims 1-30 are pending.

Claims 3 and 14-30 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1, 2, and 4-13 are currently under consideration.

Claim Objections

Claims 2 and 12 are objected to for being drawn to unelected inventions. Claims 2 and 12 recite MITF and TRP-2 of the unelected inventions. Unelected inventions of groups III-IV comprise methods of amplifying and detecting metastatic melanoma comprising amplifying nucleic acid targets from a panel of marker genes comprising MITF and TRP-2. Appropriate correction that would remove combinations found in unelected inventions from the claims, thus restricting the claims to the elected invention, is required.

Claim 10 is objected to for an apparent typographical error. Claim 10 recites: "...at least three-year period...". It is believed that Applicant meant the claim to recite: "...at least a three-year period...". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1, 2, and 4-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 12, and dependent claims 2, 4-11, and 13, are indefinite because claims 1 and 12 are incomplete for omitting essential steps, such omission amounting to a gap between the steps. Claims 1 and 12 recite "a method of detecting metastatic melanoma cells in a patient comprising....detecting the presence or absence of the nucleic acid targets"; however, the claims do not indicate how the presence *or* absence of specific targets is to be correlated with the presence of metastatic melanoma cells. For example, the claims do not indicate whether an increase or a decrease in expression of each target gene would be characteristic of metastatic melanoma cells. Thus, there are missing steps involving correlating the detection of amplified targets to the determination of whether a sample comprises metastatic melanoma cells. See MPEP § 2172.01.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, and 4-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

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which it pertains, or with which it is most nearly connected, to make and/or use the invention as broadly claimed.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of detecting metastatic melanoma cells in a sample or tissue comprising isolating nucleic acid from *any* kind of biological sample or tissue obtained from a patient and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, tyrosinase, and MAGE-A3. The claims are further drawn to determining a patient's prognosis and assigning an AJCC stage to the patient. The claims are further drawn to selecting a treatment regime for a patient based on said prognosis.

The specification discloses a method of detecting metastatic melanoma in a sample comprising isolating nucleic acids from *sentinel lymph nodes* obtained from a patient and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, and MAGE-A3, wherein an increase in said targets, as compared to normal controls, indicates said sample comprises metastatic melanoma cells (Example 11). Further, the specification demonstrates that an increase in recurrence and a decrease in survival correlate with an increase in the number of target genes with elevated expression in patients that are histopathologically negative for metastatic melanoma (Example 11).

As taught by the specification, sentinel lymph nodes are the first nodes that receive metastatic melanoma cells and sentinel lymph nodes reflect the status of the entire lymphatic basin (page 3 lines 17-19, in particular). However, the specification lacks working examples of methods of detecting metastatic melanoma in samples other than sentinel lymph nodes. Further, it is unclear how metastatic melanoma cells could be detected in samples from regions where melanoma cells do not metastasize. Further, the specification does not demonstrate that skin samples from primary non-metastatic lesions and samples containing metastatic melanoma cells display different expression profiles for the target genes. Since GalNAcT, PAX3, MART-1, and MAGE-A3 mRNAs are “frequently found in melanomas” and were found to be expressed in *all* melanoma cell lines tested (see page 12 lines 3-7 of the specification, in particular), one of skill in the art would conclude that the claimed method would mistakenly identify

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“non-metastatic” melanoma cells as “metastatic” cells in skin samples of primary tumors. This conclusion is further supported by the teachings of Kuo et al (February 1998, Clinical Cancer Research, 4:411-418). Kuo et al teach that, not unlike samples with metastatic melanoma cells, five of nine *primary* melanoma biopsies were found to be positive for GalNAcT mRNA expression (page 413 right column of Kuo et al). Further, the claims are drawn to a method of detecting metastatic melanoma cells comprising determining the “presence or absence” of specific nucleic acid targets in a biological sample without comparing the expression level to normal controls. Although the specification teaches a significant difference in mRNA copy number between samples with and without metastatic melanoma cells, a complete lack of mRNA in either sample has not been demonstrated (Example 11, in particular). One of skill in the art would recognize that samples with only two mRNA target *molecules*, which appear to represent samples with a total lack of expression in Example 11, actually represent the “presence” of a target mRNA. Thus, one of skill in the art would recognize the importance of using a normal control in the claimed method to detect an increase or decrease in expression rather than a “presence or absence” of expression. Further, the specification and the state of the art only provide guidance, working examples, or exemplification that the claimed method would determine whether a patient has AJCC stage I or stages II-IV metastatic melanoma (see instant claim 8 and Table 3 of Kuo et al, in particular). The specification and state of the art provide no guidance, working examples, or exemplification for how the claimed method would differentiate between stages II-IV. Further, the specification lacks guidance, workable examples, or

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exemplification demonstrating how expression of the target genes is indicative of any prognosis other than disease recurrence or survival. Further, the specification provides no guidance, workable examples, or exemplification demonstrating how detecting the expression of the target genes in a sample could be used to “select” any particular treatment regime from those commonly used to treat any metastatic melanoma.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed. Thus, while the specification is enabling for a method of detecting metastatic melanoma cells in a sample comprising isolating nucleic acid from *sentinel lymph nodes* obtained from a patient and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein an increase in expression of said targets, as compared to corresponding normal controls, is indicative of metastatic melanoma, an increase in disease recurrence, and a decrease in patient survival, the specification lacks reasonable guidance, predictability, and objective evidence that enables a method of detecting metastatic melanoma cells comprising isolating nucleic acid from *any* kind of biological sample obtained from a patient and amplifying nucleic acid targets comprising GalNAcT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein the “presence or absence” of the targets is indicative of metastatic melanoma or wherein expression of the target genes is indicative of any prognosis other than disease recurrence or survival. Further, the specification lacks reasonable

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guidance, predictability, and objective evidence that the claimed method enables one to differentiate between all AJCC stages. Further, although the specification and prior art enables one to treat patients diagnosed with metastatic melanoma by conventional methods, the specification and the prior art do not enable one to “select” a particular treatment regime from those that are conventionally used in the art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuo et al (February 1998, Clinical Cancer Research, 4:411-418).

The claims are drawn to a method of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising GaINAcT and detecting the presence or absence of the nucleic acid targets. The claims are further drawn to a method wherein the biological samples are frozen lymph nodes. The claims are further drawn to predicting a patient's prognosis. The claims are further drawn to a method wherein the patient's prognosis is predicted for at least a three-year period following a removal of a primary tumor, sentinel lymphadenectomy, or both. The claims

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are further drawn to a method comprising a step of selecting a treatment regimen based on the patient's prognosis.

Kuo et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising GalNAcT and detecting the presence or absence of the nucleic acid targets (page 413 right column, in particular). The biological samples used in some of the methods taught by Kuo et al were frozen sentinel lymph nodes (page 412 left column, in particular). The methods taught by Kuo et al further comprise a step of assigning an AJCC stage to the patient based on the presence or absence of the nucleic acid targets in the sample (page 413 right column, Table 2, Table 3, and paragraph bridging pages 416-417, in particular). However, although the method of Kuo et al would differentiate between stage I and stages II-IV, the method does not differentiate between stages II, III, and IV. Since the method taught by Kuo et al only detected GalNAcT in tumor samples and not in normal samples (see Table 3, in particular), one of skill in the art would recognize that the methods would predict a patient's prognosis based on a patient having metastatic melanoma or not having metastatic melanoma for at least a three-year period. Kuo et al further teaches methods comprising a step of selecting a conventional treatment regimen based on a patient's prognosis of having metastatic melanoma (page 417 left column, in particular).

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Scholl et al (Cancer Research, 2/1/01, 61:823-826).

The claims are drawn to a method of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising PAX3, tyrosinase, and MAGE-A3, and detecting the presence or absence of the nucleic acid targets.

Scholl et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising PAX3, MAGE-A3, and tyrosinase and detecting the presence or absence of the nucleic acid targets (Table 1 and Table 2, in particular).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

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the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, and 4-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palmieri et al (March 2001, Journal of Clinical Oncology, 19(5):1437-1443) in view of Kuo et al (February 1998, Clinical Cancer Research, 4:411-418), Scholl et al (February 2001, Cancer Research, 61:823-826), and Danenberg et al (US 2001/0029018 A1; 10/11/01).

The claims are drawn to a method of detecting metastatic melanoma cells comprising isolating mRNA from a biological sample obtained from a patient, amplifying mRNA targets from a panel of marker genes comprising GaINAcT, PAX3, MART-1, tyrosinase, and MAGE-A3, and detecting the presence or absence of the nucleic acid targets. The claims are further drawn to methods wherein the mRNA targets are amplified using qRT-PCR. The claims are further drawn to a method wherein the biological samples are selected from the group consisting of paraffin-embedded melanoma tissues, frozen lymph nodes, and paraffin embedded lymph nodes. The claims are further drawn to methods wherein the biological sample is histopathologically

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negative for melanoma cells, wherein the histopathology is determined by hematoxylin and eosin staining or immunohistochemistry. The claims are further drawn to predicting a patient's prognosis. The claims are further drawn to a method wherein the patient's prognosis is predicted for at least a three-year period following a removal of a primary tumor, sentinel lymphadenectomy, or both. The claims are further drawn to a method comprising a step of selecting a treatment regimen based on the patient's prognosis.

Palmieri et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, using RT-PCR to amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase, and detecting the presence or absence of the nucleic acid targets (pages 1438-1439, in particular). The biological samples used in the methods taught by Palmieri et include paraffin-embedded melanoma tissues, frozen sentinel lymph nodes, and paraffin embedded sentinel lymph nodes (Figure 1, in particular). The methods taught by Palmieri et al comprise methods wherein the biological samples are histopathologically negative for melanoma cells (paragraph bridging the left and right columns of page 1438), wherein the histopathology is determined by hematoxylin and eosin staining and immunohistochemistry. Since the method taught by Palmieri et al only detected MART-1 and tyrosinase in tumor samples and not in normal samples (Figures 1 and 2, in particular), one of skill in the art would recognize that the methods would predict a patient's prognosis based on having metastatic melanoma or not having metastatic melanoma. Palmieri et al teaches that this prognosis would be predicted for

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at least a three-year period (page 1442 right column, in particular). Although the method of Palmieri et al would differentiate between stage I and stages II-IV, the method does not differentiate between stages II, III, and IV (Figure 1, in particular). Palmieri et al further teaches a method comprising preparing paraffin embedded samples from tissues or lymph nodes of a patient, deparaffinizing the paraffin embedded samples, isolating nucleic acid from the deparaffinized samples, and amplifying MART-1 and tyrosinase (pages 1438-1439). Palmieri et al further teaches that multiple-marker assays are more sensitive and specific than single-marker assays in detecting circulating metastatic melanoma metastases (page 1441 right column, in particular). Palmieri et al further teaches detecting metastatic melanoma using the method they describe "could improve disease management and help to obtain maximal therapeutic benefit from adjuvant therapies" (paragraph bridging pages 1441-1442).

Palmieri et al does not specifically teach methods of detecting melanoma cells comprising amplifying GalNAc, PAX3, or both GalNAc and PAX3 (claim 1), detecting MAGE-A3 (claim 2), methods comprising a step of selecting a treatment regimen based on the patient's prognosis (claim 11), or methods wherein the mRNA targets are amplified using qRT-PCR (claims 4 and 13). However, these deficiencies are made up in the teachings of Kuo et al, Scholl et al, and Danenberg et al.

Kuo et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying

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nucleic acid targets from a panel of marker genes comprising GalNAcT and detecting the presence or absence of the nucleic acid targets (page 413 right column, in particular). Kuo et al further teaches methods comprising a step of selecting a conventional treatment regimen based on the patient's prognosis (page 417 left column, in particular).

Scholl et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising PAX3, MAGE-A3, and tyrosinase and detecting the presence or absence of the nucleic acid targets (Table 1 and Table 2, in particular).

Danenberg et al teaches methods of detecting a gene overexpressed in cancers by deparaffinizing samples and using qRT-PCR to amplify said gene for detection (paragraphs 51-54, in particular).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to detect metastatic melanoma cells detecting Mart-1 and tyrosinase as taught by Palmieri et al, detecting GalNAcT and selecting a treatment regimen as taught by Kuo et al, detecting PAX3 and MAGE-A3 as taught by Scholl et al, and using qRT-PCR as taught by Danenberg et al to amplify each target gene before detection. One would have been motivated to detect all three of the target genes

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because Palmieri et al teaches that multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma metastases (page 1441 right column, in particular). Further, one would have been motivated to select a conventional treatment regimen as taught by Kuo et al because Palmieri et al teaches that detecting metastatic melanoma using multiple marker assays “could improve disease management and help to obtain maximal therapeutic benefit from adjuvant therapies” (paragraph bridging pages 1441-1442, in particular). Further, one would have used qRT-PCR, as taught by Danenberg et al, to amplify each of the three genes because qRT-PCR was known to one of skill in the art to provide results more quantitative than non-real-time RT-PCR. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed method since multiple-marker PCR assays, methods of correlating a prognosis to a treatment, and qRT-PCR are well known and conventional in the art.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

A handwritten signature in black ink, appearing to read "Gary B. Nickol".

**GARY B. NICKOL, PH.D.
PRIMARY EXAMINER**